P/42-60

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Patent Application of:

Fabrizio Samaritani et al. Date: April 12, 1999

Serial No.: 08/737,633 Group Art Unit: 1646

Filed: November 15, 1996 Examiner: D. Fitzgerald

For: IFN-BETA LIQUID FORMULATIONS

APPEAL BRIEF TRANSMITTAL LETTER - FEE COMPUTATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith in triplicate is an Appeal Brief in the above-identified application.

OFGS Check No. 83729, which includes the fee of $300.00, is enclosed.

In the event the actual fee is greater than the payment submitted or is inadvertently not enclosed or if any additional fee during the prosecution of this application is not paid, the Patent Office is authorized to charge the underpayment to Deposit Account No.
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If this communication is filed after the shortened statutory time period had elapsed and no separate Petition is enclosed, the Commissioner of Patents and Trademarks is petitioned, under 37 C.F.R. §1.136(a), to extend the time for filing a response to the outstanding Office Action by the number of months which will avoid abandonment under 37 C.F.R. §1.135. The fee under 37 C.F.R. § 1.17 should be charged to our Deposit Account No. 15-0700.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed: Assistant Commissioner for Patents, Washington, D.C. 20231, on April 12, 1999:

Charles C. Achkar
Name of applicant, assignee or Registered Representative

Charles Achkar
Signature

April 12, 1999
Date of Signature

EAM/CCA:lac

Respectfully submitted,

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P/42-60 (PCT)

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#17
B.G.J
4/22/99

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF UNDER 37 C.F.R. §1.192

Sir:

This appeal concerns the propriety of the Examiner's final rejection of all pending claims in this application.

Real Party in Interest

The assignee of this application is Applied Research Systems ARS Holding N.V.

Related Appeals and Interferences

There are no known related appeals or interference proceedings.

Status of Claims

The claims pending in this application are numbers 1 and 3-10 and all are the subject of this appeal. All other claims which at any time were pending in this case have been cancelled.

Status of Amendments

The February 27, 1998 Amendment has been entered in part. Specifically, the amendments to the claims have been entered. Also substitute pages corresponding to pages 2 and 3 of

the specification have been entered while substitute page corresponding to page 1 of the specification has not been entered because it contain an insertion of a word which was not present in the specification papers as filed. Applicants are submitting concurrently an Amendment forwarding substitute page 1.

Summary of Invention

Disclosed in this application is a stable, liquid pharmaceutical formulation consisting of interferon-beta, a stabilizing amount of mannitol, a buffer capable of maintaining the pH of the formulation at a value between 3.0 and 4.0 and, optionally, albumin.

Issues

All claims are rejected under 35 U.S.C. §103 over Cymbalista '454 as taken in view of Hershenson '605 and Rideout '232. The Examiner alleges that it would be obvious to formulate a β-IFN composition containing mannitol as the sole polyol because both Cymbalista and Hershenson teach that mannitol stabilizes β-IFN and Cymbalista exemplifies the preparation of a stable formulation comprising only one polyol. The Examiner also alleged that it would be obvious to formulate such composition without glycerol and PEG because Cymbalista evidences that such components were not necessary to obtain a stable β-IFN formulation, and Hershenson contains no teaching to the contrary.

Furthermore, the Examiner stated that Rideout teaches that pharmaceutical formulations that contain IFN may be in the form of a sterile, aqueous solutions containing buffers.

Grouping of Claims

Rejected claims 1, 3, 4, and 6-10 stand or fall together while rejected claim 5 does not stand or fall together with any of the other rejected claims for the reasons set forth in the Argument section of this Brief.

Argument

Claim 1 in this application sets forth a stable, liquid pharmaceutical formulation consisting of β-IFN, a stabilizing amount of mannitol, a buffer maintaining the pH at between 3 and 4 and, optionally, albumin. This is neither taught nor suggested by the references whether considered alone or in combination.

The Cymbalista reference relates to a method of stabilizing β-IFN with polyvinyl pyrrolidone (PVP). The only material taught to function as a stabilizer in this reference is the PVP. Furthermore, the stability data in this patent relates to the lyophilized composition and not to the liquid formulation which exists either before or after lyophilization. Any conclusion concerning the stability of those liquid formulations based on the Cymbalista disclosure is mere speculation.

It is alleged by the Examiner that it would be obvious to formulate a β-IFN composition containing mannitol as the sole polyol because Cymbalista teaches mannitol stabilizes β-IFN and exemplifies the preparation of a stable formulation comprising only one polyol. As to the first of these assertions, the Cymbalista reference has been carefully reviewed and no teaching which states or even implies that mannitol stabilizes β-IFN could be found.

As to the latter assertion, it is respectfully submitted that the characterization of mannitol as being a "polyol" constitutes a revision of the disclosure of the reference to such an extent that it has altered, impermissibly, the teachings of the reference. Medtronic, Inc. v. Cardiac Pacemakers, Inc., 220 USPQ 97 (Fed. Cir. 1983). There is nothing in the reference which characterizes mannitol as a polyol or indicates, for that matter, that the composition should contain a "polyol" for any purpose. Had Cymbalista said make a composition containing a polyol, then the fact that mannitol is a polyol may

have had some significance, but there is no such teaching. The only function attributed to mannitol by Cymbalista is that of an excipient. While it is true that the reference "exemplifies the preparation of a stable formulation comprising only one polyol", it is respectfully submitted that this after-the-fact attempted justification is not relevant since Cymbalista teach that the only reason that the formulation is stable is that it contains PVP and does not suggest using a single polyol (even if an exemplified composition can be, by hindsight, so characterized).

The Examiner also stated that Hershenson suggests that mannitol or HSA, alone or in combination, would reasonably be expected to stabilize IFN-β in the absence as well as the presence of glycerol or PEG. However, the Examiner acknowledged that Hershenson is silent on the use of formulations which lack glycerol or PEG but still maintained that the reference provides no evidence which teaches that IFN-β would not be stable absent such components.

As the Examiner has recognized, Hershenson teaches that a stabilizing amount of either glycerol or polyethylene glycol (PEG) must be present and applicants maintain that there is nothing in the reference which suggest that other materials (such as mannitol) can function as a stabilizer **in the absence** of either glycerol or PEG. Furthermore, applicants maintain that Hershenson's teachings are based on the generally known fact polyethylene glycols and glycerol are commonly used chemically stable vehicles in the liquid formulation of stable parenteral dosage forms. As further evidence of the unobviousness of using mannitol alone to stabilize INF-β, the Board is directed to Tables 4 and 5 of the specification on pages 10 and 11 where it can be noticed that the compounds commonly used in the art as "stabilizers" (such as mannitol, sucrose and glycine) have different effect on the stability of INF-β. Therefore, one

cannot predict the stabilizing effect of any of these agents alone on any particular protein without testing it beforehand.

The Examiner attempts to obviate the required presence of glycerol and PEG by asserting that "Cymbalista evidences that such components were not necessary to obtain a stable IFN-β formulation, and Hershenson contains no teachings to the contrary". However, to the extent it can be argued that the Cymbalista reference "evidences" such components are not necessary, it is only because the patentee uses PVP as a stabilizer. It is also respectfully pointed out that silence in a reference is an inadequate disclosure of facts upon which a conclusion of obviousness may justifiably follow. In re Burt, 148 USPQ 548 (CCPA 1966); In re Newell, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

In addition, applicants point out that the use of acetate buffer (as specified in claim 5) brings in additional unexpected stabilization results when compared with other buffers such as citrate, ascorbate and succinate (see specification on pages 7-9, Tables 1-3). There is nothing in the prior art that discloses or suggest that the use of citrate buffer along with mannitol brings additional stabilizing effect to INF-β.

It is assumed that the Examiner is relying on the Rideout reference for the teaching that pharmaceutical formulations that contain IFN may be in the form of sterile, aqueous solutions that contain buffers and that these solutions may be sealed in ampules or vials, as set forth on page 5 of the May 1997 Office Action. No other relevancy to the rejection is apparent and it is clear, therefore, that this additional reference does not cure any of the basic deficiencies in Cymbalista or Hershenson, whether considered alone or in combination.

Conclusion

As demonstrated above, none of the references teach or suggest alone or in combination.

Reversal of the final rejection and allowance of this application is, therefore, respectfully solicited.

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Charles C. Achkar
Name of applicant, assignee or Registered Representative

Charles Achkar
Signature
April 12, 1999
Date of Signature

Respectfully submitted,

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New York, New York 10036-8403
Telephone: (212) 382-0700

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A P P E N D I X

The Claims on Appeal Are:

1. A stable, liquid pharmaceutical formulation consisting of interferon-beta, a stabilizing amount of mannitol, a buffer capable of maintaining the pH of the formulation at a value between 3.0 and 4.0 and, optionally, albumin.

3. A liquid pharmaceutical formulation according to claims 1, in which interferon-beta is recombinant.

4. A liquid pharmaceutical formulation according to claim 1, in which interferon-beta is in a quantity between 0.6 and 1 MIU/ml.

5. A liquid pharmaceutical formulation according to claim 1, in which the buffer solution is acetate buffer.

6. A liquid pharmaceutical formulation according to claim 4, in which the buffer solution has a concentration of 0.01 M.

7. A liquid pharmaceutical formulation according to claim 1, which also comprises human albumin.

8. A liquid pharmaceutical formulation according to claim 1, comprising 1 MIU/ml of interferon-beta, 54.6 mg/ml of mannitol, 0.5 mg/ml of albumin in a solution of 0.01 M acetate buffer at pH 3.5

9. Process for the preparation of a liquid pharmaceutical formulation according to claim 1, comprising the dilution of interferon-beta with a solution of excipients.

10. A container hermetically sealed in sterile conditions comprising the liquid pharmaceutical formulation according to claim 1 and appropriate for storage prior to use.

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P/42-60 (PCT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No. 08/737,633
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